

http://www.pharmacy.wsu.edu/courses/PharS531/Parenterals%20I_files/image002.jpg

Introduction to Drugs and Medicines

Chemotherapy is the treatment of disease by use of chemicals. A **drug** is a substance that affects bodily processes. A drug is often defined as any substance taken to change the way the body or the mind functions.

The definitions of drugs and medicines are not uniform across cultures. In some societies the terms drug and medicine are interchangeable. In others drugs are considered harmful and medicines beneficial. Generally a drug or medicine is any chemical which does one or more of the following:

- alters physiological state, including consciousness, activity level or coordination.
- alters incoming sensory sensations
- alters mood or emotions

Drugs:

- may or may not come from doctors or drug stores/pharmacies
- may or may not have beneficial medicinal properties
- may come from plants or fungi or may be manufactured in laboratories
- can be legal or illegal,
- can be helpful or harmful

Drugs are divided into categories depending on their effects. These include infection fighters (antiseptics, antibiotics, antivirals), those effecting body chemistry or metabolism (hormones, vitamins), and those affecting the central nervous system (CNS) including the brain (stimulants, depressants, analgesics, anesthetics).

The Placebo Effect

Pharmacologically inert substances sometime produce significant reactions because of what an individual expects, desires or was told would happen.

A **placebo** is an inert substance used as a control in an experiment, or given to patients for its probable beneficial effects (i.e. 'fake' therapy without any side effects). Why a 'sugar pill' should be effective is not completely known, but does suggest the importance of the body's natural healing processes. For example, researchers have found that asthmatics dilated their own airways when told they were inhaling asthma medicine. The action of placebos implies the power of suggestion. Some researchers believe the placebo effect to be psychological, namely what counts is the reality present in the brain.

Research, Development and the testing of new Drugs

The development of new medicines is lengthy, and very costly process which is rigidly controlled. Most countries require drugs to be subjected to thorough laboratory and clinical studies that demonstrate their usefulness and safety. Before human studies are permitted, the

drugs are extensively tested on animals and cell cultures. These include establishment of the range of effective doses, the doses at which side effects occur and the lethal doses in various animals. Because of differences between species of animals, it may be taken into initial clinical trials (phase 1) on volunteers as well as on patients, aimed at establishing the drug's safety, a drug is subjected to thorough clinical evaluation (phase 2) to eliminate variables such as response and investigator bias. Statistical validation is critical at this stage. Finally if the drug looks promising, it enters human studies with extended clinical evaluation (phase 3). Most new drugs never get approval for marketing! Most drugs on the legitimate market have reasonable risk/benefit ratios. No drug is completely without risk, but most legal drugs should be relatively safe.

In 1970, 3620 drugs were tested, 16 came on the market at a cost of \$20 million each and after a six-year approval period. In September, 1991, a drug approved for marketing in the USA was estimated to cost \$200 million! According to *New Scientist* (INSIDE SCIENCE, #65, 16 October 1993, p1) "Bringing a new drug onto the market is a gamble-it takes on the average 12 years of research and development, and an investment of £125 million. Fewer than five out of ten thousand potential medicines ever reach a hospital or chemists' shops".

Thalidomide is an example of what can go wrong. It was marketed outside North America in the late 1950s and early 60s. It was first introduced in (the then West) Germany in 1957, and was prescribed to pregnant women to treat morning sickness. However, its use resulted in the birth of thousands of deformed babies because thalidomide prevented the proper growth of the fetus. Thalidomide is now approved in several countries including Brazil, Mexico and the US to treat the painful, disfiguring skin sores associated with leprosy, and to prevent and control the return of these skin sores. However, the medicine comes with special warnings about the severe birth defects or death to an unborn baby. Birth defects include babies with no arms or legs, short arms and legs, missing bones and intestinal abnormalities.

Methods of Administration

Transporting a drug into the body is a complex process. Administration of a drug involves introducing a drug into the blood stream. The entire blood volume (approximately 6 liters) circulates in the body about once a minute and drugs are fairly evenly distributed throughout the blood. There are several ways of administering a drug-each has advantages and disadvantages. Also, different effects can be seen depending on the route of administration. The four main methods are: oral, rectal, inhalation and parenteral (by injection).

1. Oral, i.e. by mouth:

This is very convenient. However the effect is variable since the rate of absorption is influenced by, for example, drug concentration and stomach content. Absorption takes place along the entire gastrointestinal tract from the mouth to the intestine. The percentage absorption of a drug in the stomach is generally small, except for alcohol, about one third of which is absorbed. For most drugs taken orally, the **primary site of absorption** is the small intestines which are also the site of absorption of digested food. A drug that is difficult to dissolve will be absorbed slowly.

Time-release capsules have various coatings to ensure gradual release of the drug over time. The form in which a drug is available, as a tablet or in liquid form, and whether it is taken on an empty stomach or with food determines the rate at which the drug is absorbed.

2. Rectal, i.e. via the rectum:

This method of administration is very effective when patients experience nausea or vomiting or are unable to take medication orally before or after surgery. Drugs that are pH sensitive and that may be destroyed by the stomach's acidity may be delivered rectally. A drug capsule of systemic effect – one that affects any part of the body – can be inserted into the rectum in the form of suppositories. The drug is then absorbed into the blood stream. Suppositories for the relief of hemorrhoids (enlarged and painful blood vessels in or around the anus) are used for local effect.

3. Inhalation, i.e. breathing in:

Administration is rapid because of the extensive network of blood vessels in the lungs. Drugs administered by this route to produce a systemic effect (such as general anesthesia) in which the drug is absorbed into the blood stream to produce an effect in the brain and the whole body. Patients suffering from asthma achieve quick relief from the use of drugs such as Ventolin™ that dilate the respiratory tract.

4. Parenteral, i.e. by injection:

- a. Beneath the skin (subcutaneous route): Drug absorption is slower than intravenous (directly into a vein). Dental injections are often subcutaneous. The method is also common with illegal drug users.
- b. Into muscles (intra-muscular): For use when immediate response is not required or when a large volume of drug needs to be injected. The method is relatively safe and easy provided a blood vessel is not accidentally penetrated. Many vaccination injections e.g. for overseas travel, are intra-muscular.
- c. Directly into the blood stream (intravenous). This is the most practical; the drug is introduced by injection into a vein and distributed around the body within about a minute, so the effect is virtually instantaneous. An advantage is that it is possible to administer precise amounts of drug since concentration is not affected by stomach acid or content. However, once administered, the drug cannot be retrieved as it can (to some extent) with oral administration.



Except for intravenous injections, a drug must be transported across the blood vessels, which contain a fatty or lipid layer. Drugs which dissolve readily in fat are therefore more easily absorbed. Drugs can be absorbed into the blood stream from a region of high to low drug

concentration, by osmosis. The capillaries of the brain are denser and prevent diffusion of many substances into the neurons of the brain – that is called the blood-brain barrier and is very important. For example, penicillins do not pass this barrier. This is fortunate since they cause convulsions if injected directly into the brain. Psychoactive drugs have to pass into the brain as these drugs alter behaviour or change consciousness.

Termination of a drug's action takes place when it is broken down by the liver and eliminated by the kidneys. **Half-life** is the time required for half the drug to be eliminated. For example, the half life of cocaine is a few minutes, but marijuana can be detected up to 28 days after use – it is absorbed by fatty tissue and bound to it making diffusion into the blood stream a very slow process.

Lethal dosage (LD₅₀), tolerance, and side effects.

A toxic substance (poison) is a chemical that is dangerous or causes illness or death (lethal effect) in small amounts. An example is the nerve gas sarin used in the Tokyo subway incident which was found to be extremely toxic in minute quantities. Substances such as nicotine can be moderately toxic to animals, whereas water is considered almost completely non-toxic. The lethal dose for a toxic substance varies from chemical to chemical and from one individual and/or species to another. Thus, lethal doses of poisons are expressed as milligrams of toxic substance per kilogram of body mass of the animal.

An LD₅₀ (lethal dose in 50% of the population) value is used to indicate the dose of a given toxic substance in mg per kg body mass that kills 50% of the laboratory animals under study such as rats, mice and guinea pigs. The smaller the value of LD₅₀, the more toxic the substance. Since different species react differently to various poisons, any such data based on animal studies to human beings must be used with caution. Thus, studies are often carried out with different animals before such extrapolation is made. Dosage is an important principle of toxicology.

On the basis of such studies, heroin has an LD₅₀ of between 1 and 5 mg/kg. This means that a 75 to 375 mg dose of heroin will be fatal to 50% of average people weighing 75 kg.

Examples of approximate LD₅₀ values

Toxic Substance	LD₅₀ (mg substance/kg body mass)	Degree of toxicity
Botulism Toxin	<0.01	Extremely toxic
Potassium cyanide	Between 1 and 5	Highly toxic
Morphine	Between 5 and 50	Highly toxic
Aspirin, sulfuric acid	Between 50 and 500	Toxic
Amphetamine, nicotine	Between 500 and 5000	Moderately toxic
Ethanol, soap	Between 5000 and 15000	Slightly toxic

The degree of toxicity is sometimes defined as the mass of substance required for a lethal dose, but

this tends to vary between countries. Drugs can be considered hazardous when they pose risks to the physical, mental, or social well-being of the user.

Dependence

Some people use drugs because they have become physically or psychologically dependent on them. When an individual continues to use a certain drug because s/he does not feel 'right' without it, that person can be said to be drug-dependent.

Physical Dependence

Physical dependence occurs when a drug user's body becomes so accustomed to a drug that it can only function normally if the drug is present. Without the drug, the user may experience a variety of physical symptoms ranging from mild discomfort to convulsions. These symptoms, some of which can be fatal, are referred to as 'withdrawal'. Not all drugs produce physical dependence. Physical dependence is a form of drug addiction. For example, long term use of opiates can lead to physical dependence.

Psychological Dependence

Psychological dependence exists when a drug is so central to a person's thoughts, emotions, and activities that it is extremely difficult to stop using it, or even stop thinking about it. Psychological dependence is marked by an intense craving for the drug and its effects. Like physical dependence, psychological dependence is a form of drug addiction.

Tolerance

Tolerance means that, over time and with regular use, a user needs increasing amounts of a drug to get the same psychological effect. For example, long term use of opiates can lead to tolerance. Tolerance increases the health hazards of any drug simply because the amount taken increases over time. Tolerance also increases the risk of dangerous fatal overdose for two reasons:

- Firstly, with some drugs, the drug does not necessarily develop tolerance to the harmful effects of the drug. Long-term barbiturate users, for example, become tolerant to the drug's sedative effect, but not to its side effect on breathing. If the drug is used for too long a time. The dose people need to fall asleep or calm their nerves may be more than enough to stop their breathing.
- Secondly, if a drug user has not taken the drug in a long time, the expected tolerance may have actually decreased. So after a long period of abstinence, the size of dose the user had previously become accustomed to may actually be enough to cause an overdose.

Drug Side Effects

The desired effect of a drug is considered to be the **main effect**; the unwanted responses are considered **side effects**. This happens because no drug exerts a single effect; usually several different body functions are altered. To achieve the main effect, the side effects must be tolerated which is possible if they are minor but may be limiting if they are more serious. The distinction between main and side effects is relative and depends on the purpose of the drug, e.g. morphine. If pain relieving properties are sought, the intestinal constipation induced is an undesirable side effect. However, it may also be used to treat diarrhea, so constipation induced is the main effect and any relief of pain is a side effect.

No drug is free of toxic effects, often these may be trivial but can also be serious. Allergies to drugs may take many forms from mild skin rashes to fatal shock caused by such drugs as

penicillin. Because drugs are concentrated, metabolized and excreted by the liver and kidney, damage to these is not uncommon, e.g. alcohol causes liver damage and the thalidomide tragedy dramatically illustrated that drugs may adversely influence fetal development.